REMARKS/ARGUMENTS

This preliminary amendment is made to eliminate multiple dependency and claims not in appropriate format for US prosecution. In addition, the amendments to the claims are believed to place the application in form for allowance in view of the comments in the Written Opinion issued during the PCT phase of the application. No new matter has been added.

Claim 1 has been amended to replace the term "tumorigenesis"with the phrase "initiation of primary or metastatic tumor growth." This amendment, which is supported in ¶ 31 of the application as filed, is intended to highlight a difference between the claimed invention and the art cited in the Written Opinion as discussed below. Claim 6 has been amended to refer to only breast and prostate cancer, which are the cancers for which results are specifically shown. New claim 16 is limited to a subclass of tumors in which the tumor expresses and amplified or activated version of a receptor protein kinase. This amendment is supported, inter alia, in ¶¶ 1 and 57 and throughout the examples where the relevance of kinases is discussed.

In the PCT Written Opinion, the Examiner asserted that claims 1-4, 8-10 and 12 lacked novely over US Patent Application 2003/0224993 of Land et al. Applicants respectfully disagree. Land is silent in its disclosure concerning tumorigenesis, and actually demonstrates only an ability to retard growth in soft agar. While growth is necessary for tumors to proceed, it is not sufficient as a predictor of tumorigenesis, which also requires an understanding of other properties including invasiveness. Indeed, proliferation alone done not as a general rule distinguish normal and tumor tissues. The Examiner also cited Dajee et al as anticipating claims 1 and 3. Dajee relates to tests on articially transformed cells *in vitro* that contain a Ras and a dominant negative NFkB which may be a tumor suppressor but is not an oncogene. Dominant negative NFkB is not found in human tumors so this is plainly an artificial situation which does not directly reflect in vivo therapy. Thus, neither of these experimental disclosures equates with *in vivo* therapy as claimed. Thus, the references are not anticipatory.

Furthermore, Applicants submit that the presence of apparently contradictory roles of $\alpha 6\beta 4$ in the art does not permit the extension of these tests to in vivo therapy with any expectation of success. For example, studies with established breast carcinoma cell lines have suggested that expression of b4 promotes carcinoma cell invasion through Matrigel in vitro (Shaw et al. 1997). Co-immunoprecipitation analyses suggest that a6b4 combines with the EGF-R, ErbB-2/Neu and Met RTKs, which are often mutated or amplified during tumor progression, and cell biological studies suggest that a6b4 enhances the ability of these RTKs to promote tumor cell migration in vitro (Falcioni et al. 1997; Mariotti et al. 2001; Trusolino et al. 2001). Finally, a6b4 interaction with laminin-5 increases the potential of keratinocytes transformed in vitro by activated Ras in combination with dominant negative Ik-B to form subcutaneous tumors in immunocompromised mice (Dajee et al. 2003).

Although these results suggest that deregulated joint a6b4-RTK signaling might contribute to carcinoma invasion and growth, several studies stand in stark contrast with this hypothesis. Expression of wild type but not signaling-defective b4 activates p53 and induces cell

cycle arrest and apoptosis in rectal carcinoma cells (Bachelder et al. 1999). Furthermore, antibody blockade of a6b4 enhances invasion by colon adenocarcinoma cells (Daemi et al. 2000). Finally, dominant negative inhibition of a6b4 disrupts mammary epithelial adhesion and polarity in 3-D culture (Weaver et al. 2002).

The complex and apparently contrasting effects that a6b4 exerts in different cancer cells may reflect physiologically distinct roles of the integrin in different cellular contexts or the intrinsic limitations of overexpression, dominant negative inhibition, and antibody blockade experiments. To overcome these limitations, in the experiments leading to the present invention, the inventors used genetic methods to ablate b4 signaling in mouse models of breast and prostate cancer to thus arrive at a clearer picture of the actual role of a6b4 and its validity as a therapeutic target.

For the foregoing reasons, Applicants submit that this application is now in form for allowance and such action is respectfully urged.

Respectfully submitted,

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